Malignant pleural mesothelioma: in search of new markers and therapeutic approaches

Dr Mir Alireza Hoda,
Division of Thoracic Surgery, Department of Surgery, Comprehensive Cancer Center (CCC) Vienna, Medical University of Vienna, Austria.

E: mir.hoda@meduniwien.ac.at

Assoc Prof Dr Michael Grusch,
Institute of Cancer Research, Department of Medicine I, Comprehensive Cancer Center (CCC) Vienna, Medical University of Vienna.

E: Michael.grusch@meduniwien.ac.at

Malignant pleural mesothelioma (MPM) is an aggressive malignancy arising from pleural mesothelial cells. Mesothelial cells are derived from the mesoderm and form an epithelial cell layer along the entire surface of the pleural cavity. About 80% of MPM cases are linked to asbestos exposure and its use in past decades has led to a sharp rise in incidence in recent years because of the long latent time taken for tumour induction and progression. Although the industrial use of asbestos has been banned in many countries, a global increase in MPM cases is expected due to this long latency period, and the continued production and use of asbestos in heavily populated countries, including China, India, Russia and Brazil [1].

MPM rapidly spreads as multifocal tumour nodules throughout the pleural cavity (Figure 1). Histologically, MPM either maintains an epithelioid histology, or occurs in a sarcomatoid or mixed (biphasic) form. The prognosis of MPM is dismal, with median survival of 12-14 months. Current treatments consisting of combinations of surgery, radiation therapy and cisplatin/pemetrexed chemotherapy have only a moderate effect on survival and are feasible only in a few subsets of patients. Once a patient's cancer progresses on first-line therapy, no effective second-line therapy seems to be available.

In light of this unsettling combination of rising incidence and limited therapeutic options, the search for new treatments, as well as biomarkers helping to identify patients most likely to benefit from treatment, makes it a priority.

Sparked by recent breakthroughs with immune checkpoint modulators in melanoma and non small cell lung cancer (NSCLC), immunotherapy is now a very active area of research into MPM. Several clinical trials are being conducted [2], with some promising preliminary data being reported during the recent conference of the international mesothelioma interest group (iMIG) held this October in Capetown, South Africa. Similar to other malignancies, some MPM patients may achieve long-lasting positive responses from such therapies. Due to the considerable toxicities associated with these treatments it is all the more important to identify the most likely responders.

Another very active field is targeted inhibition of proteins that drive malignant growth. Unlike NSCLC where a number of recurring targetable genomic alterations in growth promoting oncogenes like EGFR, FGFRs or ALK have been identified, genomic analysis in MPM has identified recurrent mutations mostly in genes known to be tumour suppressors [3]. The most frequently

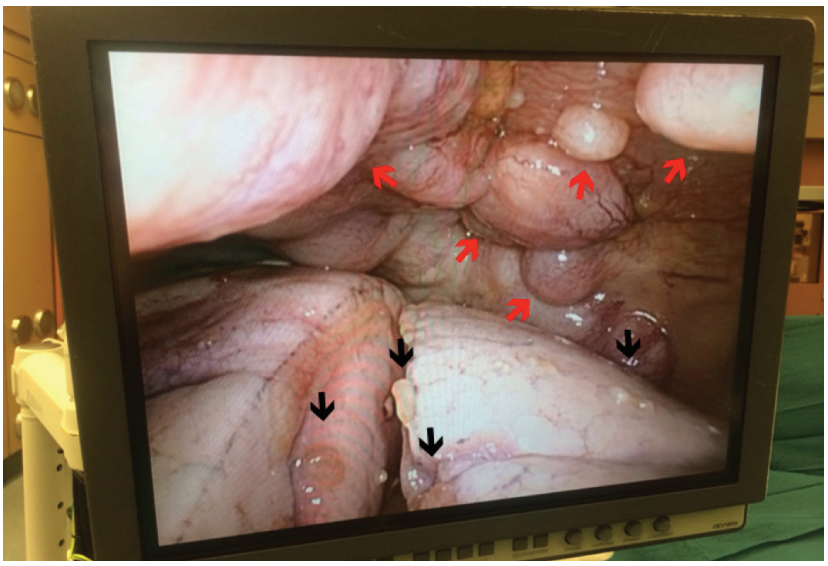
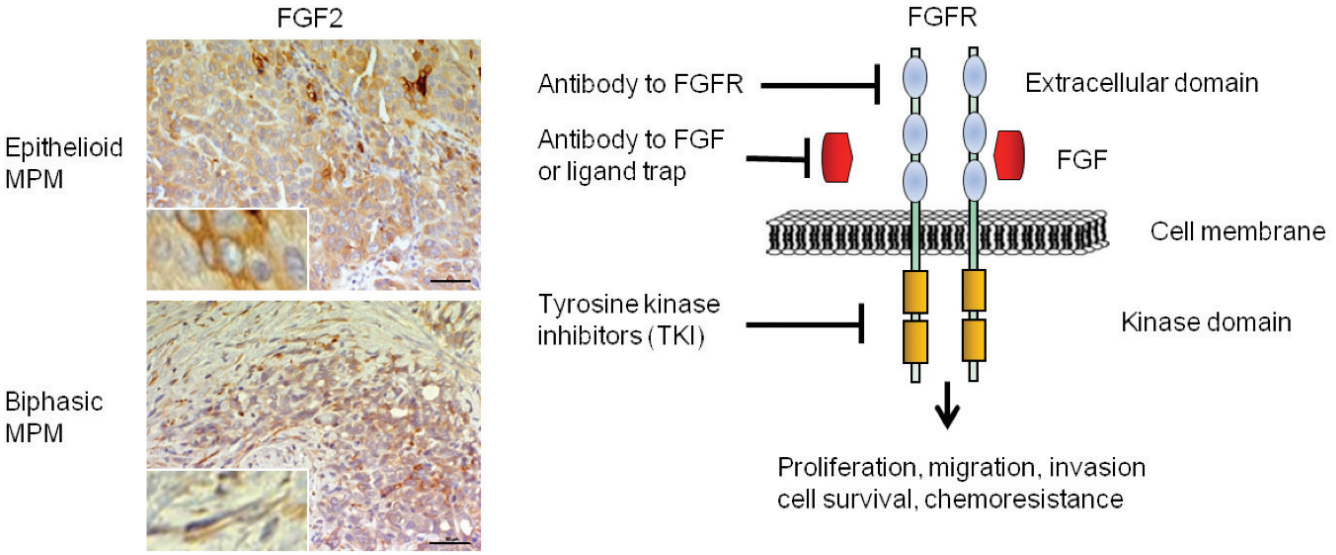


Figure 1: Video-thoracoscopic view of the left pleural space in a malignant pleural mesothelioma patient. Nodular multifocal tumour masses are visible on the parietal (red arrows) and visceral (black arrows) pleura.

Figure 2: Fibroblast growth factor (FGF) – fibroblast growth factor receptor (FGFR) axis as target in malignant pleural mesothelioma. (A) Examples of epithelioid and biphasic MPM demonstrating FGF2 immunostaining. (B) Schematic representation of different targeting approaches for FGFR. Binding of FGF to FGFR leads to receptor dimerisation and initiation of signal transduction which in turn results in enhanced cell growth, migration, invasion and chemoresistance. Inhibition approaches include blocking the intracellular kinase domain with tyrosine kinase inhibitors, targeting the extracellular domain with monoclonal antibodies or sequestering FGF ligands with monoclonal antibodies or ligand traps engineered from extracellular receptor domains.



mutated genes are BAP1, CDKN2A/2B, NF2 and TP53, which have in common that their mutations lead to a loss of function, making them less easily targetable by most conventional drugs. A frequent mutation of the TERT promoter seen in other malignancies also occurs in MPM [4]. Other growth drivers in MPM seem to be deregulated by epigenetic mechanisms independent of direct somatic mutations, amplifications or translocations. A potential target attracting a lot of interest is focal adhesion kinase (FAK). FAK inhibitor sensitivity has been linked to loss of NF2 and expression of aldehyde dehydrogenase, a putative marker of cancer stem cells [5]. In consequence, several companies are now exploring FAK inhibitors in preclinical models and clinical studies.

We have identified the signaling molecule mTOR [6] and the growth factor activin A [7], and recently the growth factor receptor, FGFR1, as potential targets for MPM therapy [8]. FGFR1 and several of its ligands are highly expressed in cell lines and tissue sections of MPM (Figure 2A), but not in normal mesothelium. Blocking FGFR1 with a kinase inhibitor or a genetic construct reduced growth and increased apoptosis in vitro and in a mouse model. A combination of FGFR1 inhibition with radiation or cisplatin was synergistic in inhibiting growth. Promising results regarding FGFR1 targeting in MPM models have also been reported by others [9]. Figure 2B shows potential approaches for targeting FGFR1 with monoclonal antibodies, kinase inhibitors or ligand traps. The clinical benefit of FGFR inhibition in mesothelioma will be addressed in a recently launched clinical trial with FP1039 (GSK3052230, Trial ID: NCT01868022), a ligand trap for FGFR ligands. An alternative therapeutic approach for targeting overactivated signaling molecules is microRNA (miRNA) replacement. MicroRNAs are small RNA molecules that regulate the expression of protein coding genes; members of the miR 15/16 family in particular are lost in MPM. Mir16 replacement inhibits growth in preclinical models of MPM [10] and a clinical trial is being initiated.

Existing and new therapies can cause severe adverse effects; they can also be expensive. Ideally each patient should receive the therapy to which he or she is most likely to respond. However, the existence of reliable biomarkers for prognosis, including prediction of the response to either classical or novel therapeutic modalities, remains a challenging task. Mesothelin is the most widely investigated diagnostic marker for MPM, but its specificity and sensitivity are limited. Mesothelin may also be a growth driver in MPM, which makes it a promising target for an immunotoxin approach [11]. Some of the favorable prognostic factors in MPM now accepted are epithelioid histology, young age and good performance status [12]. Other markers with either prognostic or predictive value, including osteopontin, fibulin-3, neutrophil to lymphocyte ratio (NLR) or ERCC1, have been proposed, but not without some controversy. Our group has identified C-reactive protein (CRP) as a predictive factor for benefit from multimodality treatment [13], and also fibrinogen as a prognostic marker and predictor of benefit from surgery within multimodality treatment [14]. These markers, however, will need validation before clinical decisions can be made.

While the outlook for patients with MPM has shown little improvement over the past few years, there is renewed hope that this could change in the not too distant future, with new therapeutic approaches currently being investigated in preclinical models and clinical trials. Immunotherapeutic approaches and new molecularly targeted inhibitors hold considerable promise, but none will be effective in all MPM patients. A combination of new treatments together with robust biomarkers is required to achieve progress that might eventually pave the way to being able to measure survival time of patients in years rather than months.

REFERENCES

1. Stayner L, Welch LS, Lemen R. *The worldwide pandemic of asbestos-related diseases.* Annu Rev Public Health 2013;34:205-216.
2. Wong RM, Ianculescu I, Sharma S, Gage DL, Olevsky OM, Kotova S, Kostic MN, Grundfest WS, Hou D, Cameron RB. *Immunotherapy for malignant pleural mesothelioma. Current status and future prospects.* Am J Respir Cell Mol Biol 2014;50:870-5.
3. Sekido Y. *Molecular pathogenesis of malignant mesothelioma.* Carcinogenesis 2013;34:1413-9.
4. Tallet A, Nault JC, Renier A, Hysi I, Galateau-Salle F, Cazes A, Copin MC, Hofman P, Andujar P, Le Pimpec-Barthes F, Zucman-Rossi J, Jaurand MC, Jean D. *Overexpression and promoter mutation of the TERT gene in malignant pleural mesothelioma.* Oncogene 2014;33:3748-52.
5. Shapiro IM, Kolev VN, Vidal CM, Kadariya Y, Ring JE, Wright Q, Weaver DT, Menges C, Padval M, McClatchey AI, Xu Q, Testa JR, Pachter JA. *Merlin deficiency predicts FAK inhibitor sensitivity: a synthetic lethal relationship.* Sci Transl Med 2014;6:237ra268.
6. Hoda MA, Mohamed A, Ghanim B, Filipits M, Hegedus B, Tamura M, Berta J, Kubista B, Dome B, Grusch M, Setinek U, Micksche M, Klepetko W, Berger W. *Temsirolimus inhibits malignant pleural mesothelioma growth in vitro and in vivo: synergism with chemotherapy.* J Thorac Oncol 2011;6:852-63.
7. Hoda MA, Munzker J, Ghanim B, Schelch K, Klikovits T, Laszlo V, Sahin E, Bedeir A, Lackner A, Dome B, Setinek U, Filipits M, Eisenbauer M, Kenessey I, Torok S, Garay T, Hegedus B, Catania A, Taghavi S, Klepetko W, Berger W, Grusch M. *Suppression of activin A signals inhibits growth of malignant pleural mesothelioma cells.* Br J Cancer 2012;107:1978-86.
8. Schelch K, Hoda MA, Klikovits T, Munzker J, Ghanim B, Wagner C, Garay T, Laszlo V, Setinek U, Dome B, Filipits M, Pirker C, Heffeter P, Selzer E, Tovari J, Torok S, Kenessey I, Holzmann K, Grasl-Kraupp B, Marian B, Klepetko W, Berger W, Hegedus B, Grusch M. *Fibroblast Growth Factor Receptor Inhibition Is Active against Mesothelioma and Synergizes with Radio- and Chemotherapy.* Am J Respir Crit Care Med 2014;190:763-72.
9. Marek LA, Hinz TK, von Massenhausen A, Olszewski KA, Kleczko EK, Boehm D, Weiser-Evans MC, Nemenoff RA, Hoffmann H, Warth A, Gozgit JM, Perner S, Heasley LE. *Nonamplified FGFR1 Is a Growth Driver in Malignant Pleural Mesothelioma.* Mol Cancer Res 2014;12:1460-9.
10. Reid G, Pel ME, Kirschner MB, Cheng YY, Mugridge N, Weiss J, Williams M, Wright C, Edelman JJ, Vallely MP, McCaughan BC, Klebe S, Brahmbhatt H, MacDiarmid JA, van Zandwijk N. *Restoring expression of miR-16: a novel approach to therapy for malignant pleural mesothelioma.* Ann Oncol 2013;24:3128-35.
11. Hassan R, Miller AC, Sharon E, Thomas A, Reynolds JC, Ling A, Kreitman RJ, Miettinen MM, Steinberg SM, Fowler DH, Pastan I. *Major cancer regressions in mesothelioma after treatment with an anti-mesothelin immunotoxin and immune suppression.* Sci Transl Med 2013;5:208ra147.
12. Mineo TC, Ambrogi V. *Malignant pleural mesothelioma: factors influencing the prognosis.* Oncology (Williston Park) 2012;26:1164-75.
13. Ghanim B, Hoda MA, Winter MP, Klikovits T, Alimohammadi A, Hegedus B, Dome B, Grusch M, Arns M, Schenk P, Pohl W, Zielinski C, Filipits M, Klepetko W, Berger W. *Pretreatment serum C-reactive protein levels predict benefit from multimodality treatment including radical surgery in malignant pleural mesothelioma: a retrospective multicenter analysis.* Ann Surg 2012;256:357-62.
14. Ghanim B, Hoda MA, Klikovits T, Winter MP, Alimohammadi A, Grusch M, Dome B, Arns M, Schenk P, Jakopovic M, Samarzija M, Brcic L, Filipits M, Laszlo V, Klepetko W, Berger W, Hegedus B. *Circulating fibrinogen is a prognostic and predictive biomarker in malignant pleural mesothelioma.* Br J Cancer 2014;110:984-90.